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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/804,166	02/20/97	CAMPBELL	

EXAMINER	
CAMPBELL, J.	
ART UNIT	**PAPER NUMBER**
1646	10

HM11/0522

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DATE MAILED: 05/22/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ ~~Responsive~~ to communication(s) filed on 3/18/98

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-14, 19 is/are pending in the application.
Of the above, claim(s) 7-13 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1-6, 14, 19 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☒ Claim(s) 1-14, 19 were ~~are~~ subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 6, 8
☐ Interview Summary, PTO-413
☒ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

Part III: Detailed Office Action

Notice: Effective February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit **1646**.

Claims 1-14 and 19 are pending and under consideration.

Applicant's election of the species TBP-1 and hCG in Paper No. 9, filed 3/18/98 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818. Claims 7-13 are withdrawn from prosecution as being drawn to non-elected species.

Formal Matters:

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The disclosure is objected to because of the following informalities:

- Applicants are advised that the ATCC has moved from Rockville, MD to Manassas, VA, effective March 23, 1998. The correct address is now:

  American Type Culture Collection
  10801 University Boulevard
  Manassas, VA 20110-2209

The specification should be amended to reflect the correct address for the ATCC.

- The Tables, which start at page 27 of the specification as filed, should be inserted into the appropriate portions of the specification, rather than being appended.

Appropriate correction is required for each item above.

Objections and Rejections under 35 U.S.C. §112:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6, 14 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, part (a) is indefinite as it is not clear whether the phrase "and fragments thereof..." refers to any of the members of the Markush group, or alternatively is only intended to modify the "ligand". The claim is further indefinite due to the use of the plural "fragments"; it is not clear how many fragments, and whether or not each individual fragment retains the stated binding capability. Similarly, in part (b) of the claim, it is not clear how many fragments are envisioned, and whether each must retain the stated dimerization ability, or whether applicants intend some set of fragments that collectively have such a property. The claim is further indefinite for stating that "sequences (a) and (b) are bonded directly"; it is not clear to what they are "bonded". Amendment to indicate that they are joined to each other would be remedial for this point. Applicants should also correct the grammatical error in the claim, which reads in part: "the sequence (b).... *are* capable". The claim should be amended to either "the sequences (b)", or "is capable".

Claim 2 uses the terms TBP1 and TBP2; such acronyms are indefinite, and should be appropriately defined at their first use in the claims. Also in claim 2, line 3 it is not clear whether "or fragments thereof" refers to only TBP2, or to both TBP1 and TBP2.

Claim 2 is further indefinite as it is not clear how antibody light chains can be capable of retaining binding capability in the absence of a heavy chain, or vice versa.

Claim 2 is also further indefinite because of the recited elements which are listed as possibilities for element (a) of claim 1 are included antibody light or heavy chains or fragments thereof, and antibody Fab domains. This is indefinite because claim 1, from which claim 2 depends,

does not include as a possibility antibody chains, as they are not receptors nor chains thereof within the meaning set forth at page 11 of the specification, nor can they be considered a ligand within the meaning set forth at page 11 of the specification.

Claims 4 and 5 are indefinite as it is not clear whether applicants are merely trying to indicate the orientation of the two sequences, or whether the claims are intended to limit to a direct linkage as opposed to a linkage involving a peptide linker.

Claim 6 is indefinite as it is not clear how the fragments "correspond" to the cited residues of TBP1.

Claim 6 is further indefinite because, although it appears that applicants intend that the hybrid protein comprises one chain comprising the hCGα subunit or fragment thereof and one chain comprising the hCGβ subunit or fragment thereof, it is not clear from the claim that such is the case.

Claim 14 is indefinite as it is not clear how the "one or more covalent bonds" are added.

The remaining claims are rejected for depending from an indefinite claim.

Rejections Over Prior Art:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5, 14 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boime, U.S. Patent number 5,705,478 .

Boime discloses single chain proteins which comprise two individual subunits of a glycoprotein hormone. The glycoprotein hormones, LH, CG, FSH, and TSH, are heterodimeric proteinaceous hormones. At column 4, Boime discloses that the protein may comprise and α and a β subunit, optionally linked with a linker moiety between the two (lines 25-29), in a head-to-head, tail-to-tail, or head-to-tail configuration (lines 34-40). At columns 12-13, Boime discloses that the linker moiety may itself have biological activity, the numerous species listed at column 13 being "ligands" within the meaning in the instant application, e.g. various cytokines and interleukins. Also at col. 13, beginning at line 15, Boime discloses the inclusion of a proteolytic cleavage site within the linker to allow release of the drug from the fusion protein. Boime differs from the instant specification in that the invention therein is directed to single chain pseudodimers, which would fold back upon themselves, rather than the proposal that the individual chains would associate with a second chain to form a heterodimer. However, a construct comprising, as suggested by Boime, and α and a β glycoprotein hormone subunit separated by a linker moiety such as (a)-ligand IFN-β, which the ordinary artisan would immediately envision given Boime's disclosure of one of "the various interferons" as a linker moiety at column 13, line 6, would necessarily form a hybrid protein as claimed, given the ability of the α and β subunits to dimerize. While the predominant resultant protein might well be a pseudodimeric protein as intended by Boime, the ordinary artisan would immediately realize that dimeric and multimeric proteins would also form, due to the interaction of (for instance) the α portion of one protein with the β portion of another. Therefore, the invention is *prima facie* obvious over the disclosure of Boime.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Capon et al., U.S. Patent number 5,116,964

Capon et al. teach hybrid immunoglobulin molecules, wherein a portion of an antibody is fused via recombinant DNA technology to a heterologous protein. At column 4, beginning at line 57, they state that the molecules are "for directing ligand binding partners such as toxins, cell surface partners, enzymes, nutrient substances, growth factors, hormones, or effector molecules...", "...to cells bearing ligands for the ligand binding partners, and for use in facilitating purification of the ligand binding

partners." At column 5, Capon et al. teach the fusion of different binding partners onto more than one chain of the immunoglobulin, to produce a multi chain polypeptide with multiple binding functions. Therapeutic and diagnostic compositions comprising the Ig fusion proteins are envisioned (column 5, line 55) . Although Capon et al. disclose both the concepts of Ig fusions comprising hormones as the 'ligand binding partner' and Ig fusions comprising two or more different ligand binding partners, they do not teach or suggest specifically Ig fusions comprising one or more subunits of a heterodimeric proteinaceous hormone.

Sledziewski et al., U.S. Patent number 5,155,027

Sledziewski et al. teach the production of biologically active peptide dimers comprising "a peptide requiring dimerization for biological activity joined to a dimerizing protein", see abstract. The dimerizing protein is disclosed as being an immunoglobulin heavy or light chain or dimerizing portion thereof, or alternatively a dimerizing protein such as yeast invertase column 3, lines 38+), acid phosphatase, yeast type I killer preprotoxin, alpha galactosidase melibiase or ornithine decarboxylase (see paragraph bridging cols. 11-12), but is not limited to such, given the definition at column 8, line 47, that the dimerizing protein is "a polypeptide chain having affinity for a second polypeptide chain, such that the two chains associated under physiological conditions to form a dimer. The second polypeptide chain may be the same or a different chain." Disclosed peptides requiring dimerization include CSF-1, TGFβ, PDGF, and factor XIII, all of which are homodimeric (see col. 10). Sledziewski et al. do not specifically teach or suggest dimers which comprise heterodimeric peptide dimers.

Ralph et al., U.S. Patent number 5,567,611

Ralph et al. disclose fusion proteins comprising M-CSF, which have M-CSF activity and at least one other bioactivity. At column 3, they disclose that the M-CSF coding sequence can be at either the amino-terminal or carboxy-terminal end of the hybrid gene, and that "since native M-CSF is a dimer, the multifunctional fusion proteins of the invention as disclosed herein occur as dimeric or higher multimeric fusion proteins" (column 3, lines 53+). At column 4, Ralph et al. teach that M-CSF can be coupled to toxins, other 'blood proteins' (those listed are all cytokines) or antibodies. Thus, Ralph et al. teach the use of a non-immunoglobulin, mammalian cytokine as a dimerizing protein in a fusion protein construct. Ralph et al. do not specifically teach the use of a heterodimeric hormone (which is a cytokine), as opposed to a homodimeric protein such as M-CSF.

Gillies, U.S. Patent number 5,650,150

Gillies discloses fusion proteins comprising an immunoglobulin heavy chain and a cytokine, such as lymphotoxin (TNFβ), IL-2, GM-CSF, etc. (see abstract, figure 1, and column 5), for the purpose of targeting the cytokine to a moiety bound by the immunoglobulin. The cytokine is fused to the C-terminus of the Ig chain (Figure 1). Also at col. 5, Gillies discloses the use of linkers, optionally including a proteolytic cleavage site for release of the cytokine at the targeted site.

Beutler et al., U.S. Patent number 5,447,851

Beutler et al. disclose chimeric polypeptides (fusion proteins) comprising the extracellular portion of a cytokine receptor attached to a portion of IgG, optionally with a cleavable peptide linker between the two. A particularly disclosed embodiment is TBP1 (55kD TNF receptor extracellular domain) attached through a thrombin sensitive linker to the Fc and hinge portion of mouse IgG1 (see abstract).

Ashkenazi et al., PNAS 88:10535, cited by applicants, discloses that TBP1-Ig fusion protein, which is dimeric, provides protection against endotoxic shock, and is superior in such to monomeric TBP1.

Advisory Information:

No claim is allowed. Claim 6 would be allowable if amended to overcome the above rejections under 35 U.S.C. §112. Although the concept of using dimeric proteins in a fusion protein to make a dimer, such as the TBP-Ig dimer of Ashkenazi et al. was known in the art, there would have been no specific motivation to make an hCG-TBP fusion.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector, whose telephone number is (703) 308-1793. Dr. Spector can normally be reached Monday through Friday, 8:00 A.M. to 4:30 P.M.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Stephen Walsh, can be reached at (703)308-2957.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 305-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. **Please** advise the Examiner at the telephone number above when an informal fax is being transmitted.

Lorraine Spector, Ph.D.
Primary Examiner

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